THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

The opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.

Paper No. 13

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

———————

Ex parte CHRISTER J. MATTSSON, CARL M. E. SVAHN
and MICHAEL P. WEBER

———————

Appeal No. 1997-2795
Application No. 08/438,933

———————

ON BRIEF

———————

Before WILLIAM F. SMITH, GRON, and SPIEGEL, *Administrative Patent Judges*.

SPIEGEL, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner finally rejecting claims 13 through 16 and refusing to allow new claim 17 and amended claim 12 as presented subsequent to the final rejection, which are all of the claims pending in this application.[1]

[1] The amendment filed August 20, 1996 (Paper No. 4), cancelling claims 8-11, amending claim 12 and adding claim 17, was entered by the examiner in the Advisory Action mailed August 29, 1996 (Paper No. 6).

Claims 14 and 17 are representative of the subject matter on appeal and read as follows:

14. Process for preparation of porcine heparin derivatives comprising

a) subjecting porcine heparin to a mild chemical sulfation,
b) oxidizing the product from step a) using periodate at pH 4-5 at 0-10E C in the dark,
c) partially depolymerizing the products from step b) using alkali,
d) reducing the product from step c) with sodium borohydrine [sic],
e) fractionating the obtained product by using gel permeation chromatography, ultrafiltration, hydrophobic interaction chromatography, affinity chromatography, ion exchange chromatography or precipitation from an aqueous solution by addition of an organic solvent,
f) collecting the product with a molecular weight not less than that of the porcine heparin used as starting material.

17. Heparin derivatives from porcine heparin obtained by the process of claim 14 and characterized by:

- having a molecular weight equal to or larger than standard porcine heparin,
- showing a sulfur content which is equal to or higher than that of said porcine heparin or at least 13% w/w,
- having an anticoagulant activity in the anti-FXa assay of less than 10% of said porcine heparin it was made from,
- showing a ratio of APTT activity over anti-FXa activity of 3-35,
- showing a reduced prolongation of bleeding time compared to said porcine heparin it was made from as measured in the rat tail after i.v. administration, and
- showing enhancement of the rate of development of coronary collaterals in dogs equal to or better than clinically used heparin.

Parallel product-by-process claim 12 and process claim 13 are drawn to heparin derivatives obtained from *bovine* heparin starting material essentially using the process of claim 14 except that the mild

chemical sulfation step is *not* performed prior to periodate oxidation of the bovine heparin starting material .

The references relied on by the examiner are:

Naggi et al. (Naggi '063)	4,727,063	Feb. 23, 1988
Naggi et al. (Naggi '881)	4,948,881	Aug. 14, 1990
Petitou et al. (Petitou)	5,013,724	May 7, 1991 (filed Jul. 11, 1986)

Casu et al. (Casu), "Retention of Antilipemic Activity by Periodate-oxidized Non-anticoagulant Heparins," Vol. 36 (I), *Arzneimittel-Forschung/Drug Research, No.* 4, pp. 637-42 (1986).

Fransson et al. (Fransson (M)), "Periodate Oxidation and Alkaline Degradation of Heparin-Related Glycans," Vol. 80, *Carbohydrate Research*, pp. 131-45 (1980).

The Merck Index (*Merck*), "An Encyclopedia Of Chemicals, Drugs, and Biologicals," page 795:4685 (Budavari et al. eds., 12th ed., Merck & Co., Inc., Whitehouse Station, NJ, 1996).[2]

Appellants rely on the following reference supplied with their brief:

"Biosynthesis of heparin and related polysaccharides" in *HEPARIN*, page 164 (Lane et al. eds., Chemical and Biological Properties Clinical Applications ed., Edward Arnolds, London, 1989) (Heparin).

[2] Merck was newly supplied by the examiner with the answer "in support of the examiner's position in the existing grounds of rejection" (Paper No. 9, page 4).

ISSUES[3]

Claims 14 and 16 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite. Claims 12 and 17 stand rejected under 35 U.S.C. § 102 as anticipated by or, in the alternative, under 35 U.S.C. § 103 as being unpatentable over any of Naggi '063, Naggi '881 or Petitou. Claims 13-16 stand rejected under 35 U.S.C. § 103 as being unpatentable over either Fransson (M) or Casu. We REVERSE.

In reaching our decision in this appeal we have given careful consideration to the appellants' specification and claims and to the respective positions articulated by the appellants and the examiner. We make reference to the examiner's answer (Paper No. 9, mailed December 13, 1996) for the examiner's reasoning in support of the rejections and to the appellants' brief (Paper No. 8, filed October 7, 1996) for the appellants' arguments thereagainst.

[3] According to the Advisory Action mailed August 29, 1996 (Paper No. 6), cancellation of claims 8-11 in the amendment filed August 20, 1996 (Paper No. 4) overcame the final rejection these claims under 35 U.S.C. § 112, second paragraph, as indefinite for lack of proper antecedent basis and under 35 U.S.C. § 103 as being unpatentable over Naggi '063, Naggi '881, Petitou, Conti (U.S. Patent No. 5,164,378, issued Nov. 17, 1992 and filed Nov. 26, 1990) or Herr (U.S. Patent No. 4,966,894 issued Oct. 30, 1990).

According to the examiner's answer, "[a]ll rejections based on HERR *et al.* (C), CONTI *et al.*(E), FRANSSON *et al.* (L and N) are hereby withdrawn, and are therefore not at issue" (Paper No. 9, page 2). Thus, the final rejection of (i) claims 12 and 17 under 35 U.S.C. § 102 as anticipated by or, in the alternative, under 35 U.S.C. § 103 as being unpatentable over Conti or Herr and (ii) of claims 13-16 under 35 U.S.C. § 103 as being unpatentable over Fransson (K) (i.e., 62 *Carbohydrate Research* 235-244 (1978), Fransson et al. (L) (i.e., 97 *FEBS Letters* 1, 119-123 (1979), or Fransson et al. (N) (i.e., 106 *European Journal of Biochemistry* 59-59 (1980)) have been withdrawn.

OPINION

I. Rejection of claims 14 and 16 under 35 U.S.C. § 112, second paragraph, as indefinite

The legal standard for indefiniteness under 35 U.S.C. § 112, second paragraph, is whether a claim reasonably apprises those of skill in the art of its scope. *See Amgen Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1217, 18 USPQ2d 1016, 1030 (Fed. Cir.), *cert. denied sub nom., Genetics Inst., Inc. v. Amgen, Inc.*, 112 S.Ct. 169 (1991). The definiteness of claim language is analyzed, not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing an ordinary level of skill in the pertinent art. *In re Moore*, 439 F.2d 1232, 1235, 169 USPQ 236, 238 (CCPA 1971).

According to the examiner, recitation of "[t]he subjective term 'mild' used to describe the sulfation in step a) of claim 14 renders the claims indefinite" (answer, page 4). To the extent the examiner's position is that "[t]he specification does not make clear what degree of 'mildness' is intended by the claims" (answer, page 9), it is untenable. Appellants are not required to specify a particular *number* as the cutoff between a "mild" and "less mild" degree of sulfation so long as appellants have provided a general guideline and examples sufficient to enable a person of ordinary skill in the art to determine whether porcine heparin is being subjected to a "mild" chemical sulfation. *In re Mattison*, 509 F.3d 563, 565, 184 USPQ 484, 486 (CCPA 1975). In our view, the specification provides a general guideline and examples which reasonably apprise the skilled artisan of the scope of

"a *mild* chemical sulfation," see e.g., page 7, lines 5-10, page 9, lines 25-33, and page 13, line 30 - page 14, line 5. For the foregoing reasons the rejection of claims 14 and 16 under 35 U.S.C. § 112, second paragraph, as indefinite is reversed.

II. Rejection of claims 12 and 17 under 35 U.S.C. § 102 as anticipated by or, in the alternative, under 35 U.S.C. § 103 as being unpatentable over any of Naggi '063, Naggi '881 or Petitou

Naggi '063 describes reacting a heparin of natural origin with a sulfuric acid/chlorosulfonic acid mixture to produce depolymerized and supersulfated heparin products having molecular weights between 2000 and 9000, with good fibrinolytic and hypolipemic activity joined to a weak anticoagulant activity (col. 4, line 67 - col. 5, line 2; col. 5, lines 41-45), and which are useful for prevention of thrombolytic diseases and treatment of atherosclerosis (col. 10, lines 58-66). Naggi '063 explicitly describes at least the relative molecular weights and degree of sulfation (a measure of sulfur content) between various starting heparin materials and their resulting product(s) and, in some cases, % elemental S (% S), results of activated partial thromboplastin time (APTT), activity towards blood coagulation factor Xa (anti-Xa activity), and the ratio anti-Xa/APTT. A summary of this data follows, with calculated APTT/anti-Xa ratios where data was available.

	mol. weight	degree of sulfation (% S)	APTT	anti-Xa activity	anti-Xa/ APTT	(calc.) APTT/ anti-Xa
starting heparin D212	13,500	1.95	1.000	1.20	1.20	0.83
product AH-16	6,000	3.0 (12.93%)	0.06	0.18	3.0	0.33
product AH-19	6,000	3.0	0.05	0.22	4.4	0.23

product AH-104	6,000	2.9 (14.54%)	0.078	0.30	3.84	0.26
product AH-103	6,000	2.8 (14.63%)				
product AH-105	6,000	3.0 (14.48%)				
product AH-106	6,000	2.8 (14.54%)	0.080	0.31	3.87	0.26
product AH-107	6,000	3.0 (14.12%)				
starting heparin D212/B	16,500	2.0				
product AH-18	3,000-5,000	2.6 (13.56%)				
starting ~~heparin~~ D212/A	10,000	1.5	0.212	0.324	1.61	0.65
product AH-17	3,000-5,000	2.5 (12.70%)	0.05	0.17	3.4	0.29
starting heparin D470	11,000	2.1				
product AH-108	6,000	3.1 (14.88%)				
product AH-109	6,000	3.0 (14.43%)				
product AH-110	6,000	2.9 (14.45%)				
product AH-111	6,000	3.0 (14.55%)				
starting heparin D98	13,500	1.8				
product AH-118	6,000	2.8 (13.90%)				
starting heparin D479	11,000	2.1				
product AH-67	4,000	2.5				
product AH-65	3,800	2.5				

product AH-68	4,500	2.8				
starting heparin Parke-Davis	19,200	2.27				
product DS-16	8,600	3.33	10% of starting heparin	60% of starting heparin	>3	

Naggi '881 describes a depolymerization and sulfation process of polysaccharides, including heparin (col. 3, lines 3-7; col. 4, lines 4-5) and shows a pattern of relative molecular weights and degree of sulfation similar to that in Naggi '063. For example, starting heparin D212 has a molecular weight of 13,500 and a 1.95 degree of sulfation while products AH-16, AH-104, AH-103, AH-105, AH-106 and AH-107 have molecular weights of 6,000 and degree of sulfations (% elemental sulfur) of 3.0 (12.93%), 2.9 (14.54%), 2.8 (14.63%), 3.0 (14.48%), 2.8 (14.54%) and 3.0 (14.12%), respectively.

Petitou describes a process of preparing highly sulfated or "sursulfated" heparin (col. 6, lines 40-49). According to the examiner, Petitou "does teach a product having molecular weight higher than 9000 daltons" (answer, page 10). However, Petitou also discloses that standard heparin has a molecular weight of 15,000 (line 4 in the table bridging cols. 17-18).

According to the examiner, the heparin derivatives described by Naggi '063, Naggi '881 or Petitou are "the same as or substantially the same as those of the instant claim[s]" (answer, page 7) or "[t]he products of the instant claims are considered to be so close to being the same as those of the

prior art as to render the instant products *prima facie* obvious to the worker of ordinary skill in the art at the time the invention was made" (answer, page 7) and, therefore, "the burden is on the appellants to show a novel or unobvious difference between the claimed products and the product of the prior art" (answer, page 8).[4] We disagree.

While the heparin derivatives of the prior art do show a sulfur content, i.e., degree of sulfation, equal to or higher than the starting heparin from which they were derived, they have molecular weights *lower* than that of the starting heparin. In fact, both the anti-Xa activities and APTT/anti-Xa ratios of the derivatives of Naggi '063, to the extent that they are disclosed, do not meet the limitations of the heparin derivatives in the claimed invention. Moreover, Naggi '063 explicitly states that it is the anti-Xa/APTT ratio which allows evaluation of "the anticoagulant component of the potential antithrombotic activity of the depolymerized and supersulfated heparins of the present invention without associated hemorragic risks" (col. 9, lines 20-24). Given the difference in anti-Xa/APTT (or APTT/anti-Xa) ratio between the heparin derivatives of Naggi '063 and the claimed derivatives in combination with the

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[4] As stated in *In re Best*, 562 F.2d 1252, 1255-56, 195 USPQ 430, 433-34 (CCPA 1977):

> Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. ... Whether the rejection is based on 'inherency' under 35 U.S.C. § 102, on 'prima facie obviousness' under 35 U.S.C. § 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products.

reliance of Naggi ‘063 on this ratio to evaluate hemorragic risk, it is unclear on what factual basis the examiner concluded that the heparin derivatives of Naggi ‘063 would impliedly have a “ ‘reduced prolongation of bleeding time’ as recited in appellants’ claims” (answer, page 5). Similarly, while the examiner relies on the background discussion in Naggi ‘881 that low molecular weight sulfated polysaccharides have been proposed as involving a weak hemorragic risk (see Naggi ‘881, col. 1, lines 26-31; answer, pages 5-6), the claimed heparin derivatives do not have a low molecular weight, but rather a molecular weight equal to or larger than that of standard bovine/porcine heparin. Furthermore, the examiner has not established a factual basis for concluding that the skilled artisan would have reasonably expected the APTT results disclosed by Petitou to correspond to the claimed reduced prolongation of bleeding time (answer, page 6). An APTT test measures the activity of the extrinsic total coagulation system (see Naggi ‘063 at col. 9, lines 10-11), whereas a bleeding time measures the activity of plasma factors, i.e., intrinsic as well as extrinsic coagulation factors, and platelet functions (see Platt, pages 225-226).[5] Thus, the examiner has not met her burden to establish that the heparin derivatives of the prior art reasonably appear to be identical or substantially identical to those of the claimed invention. *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972). Therefore, the burden has not switched to appellants to prove that the prior art heparin derivatives do not necessarily or inherently possess the characteristics of the heparin derivatives of the claimed invention.

[5] William R. Platt, “Laboratory Diagnosis of Coagulation Defects” in *COLOR ATLAS and TEXTBOOK OF HEMATOLOGY*, pages 225-26 (J. B. Lippincott Company, Philadelphia, 1969) (copy attached).

Although the examiner argues that "inherency can also play a role in a rejection under § 103" (answer, page 14), it is well established that inherency and obviousness are different concepts. *In re Shetty*, 566 F.2d 81, 86, 195 USPQ 753, 756 (CCPA 1977) ("inherency is quite immaterial if ... one of ordinary skill in the art would not appreciate or recognize that inherent result."); *In re Spormann*, 363 F.2d 444, 448, 150 USPQ 449, 452 (CCPA 1966) ("the inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown."). A conclusion of obviousness must be based on evidence, not unsupported arguments.

Based on the foregoing, we conclude that the examiner has not established that claims 12 and 17 are *prima facie* anticipated by or, in the alternative, *prima facie* obvious over any one of Naggi '063, Naggi '881 or Petitou. Having concluded that the examiner has not established a *prima facie* case of anticipation or obviousness, we do not reach appellants' discussion of rebuttal evidence on pages 7-8, 12 and 14 of the brief.

III. Rejection of claims 13-16 under 35 U.S.C. § 103 as being unpatentable over either Fransson (M) or Casu

Claims 13-16 are directed to methods of preparing heparin derivatives from porcine (claims 14 and 16) or bovine (claims 13 and 15) heparin starting material sequentially comprising (a) periodate oxidation at pH 4-5 at 0-10EC in the dark, (b) partial alkali depolymerization, (c) sodium borohydride

reduction, (d) fractionation and (e) collection of derivatives having a molecular weight not less than that of the starting heparin material. Claim 14 further requires an initial step of "subjecting porcine heparin to a mild chemical sulfation" prior to the periodate oxidation step.

Fransson (M) and Casu both describe preparing periodate-oxidized derivatives of heparin of porcine or bovine origin (in Fransson (M), see abstract and page 133, *Materials*; in Casu, see abstract and page 639, § 2.1). According to the examiner, "the sulfation of FRANSSON is considered to be 'mild'" (answer, page 15). However, the examiner has not pointed out, and we do not find, where either Fransson (M) or Casu disclose or suggest "subjecting porcine heparin to a mild chemical sulfation" prior to periodate oxidation as required by claims 14 and 16. Accordingly, we conclude that the examiner has not established a *prima facie* case of obviousness as to claims 14 and 16.

As to the remaining claims and method steps, Fransson (M) discloses periodate oxidation at *either* pH 3.0 and 4EC *or* pH 7.0 and 37EC, *either* sodium borohydride reduction *or* alkali elimination, and fractionation of the degradation products of heparin by gel chromatography (page 134, para. 2). According to Fransson (M), periodate oxidation at pH 3.0 and 4EC destroyed uronic acid residues, while periodate oxidation at pH 7.0 and 37EC produced significant cleavage of the C-2—C-3 bond in 2-amino-2-deoxy-"-D-glucose residues (page 136, first full para.). Casu discloses periodate oxidation of heparin at pH 5.3 at 4EC in the dark, followed by sodium borohydride reduction and recovery of degradation products by dialysis (page 639, § 2.1).

To establish a *prima facie* case of obviousness, there must be both some suggestion or motivation to modify the reference or combine reference teachings and a reasonable expectation of success. Furthermore, the prior art must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

According to the examiner,

> the prior art processes are considered so close to those instantly claimed that a slight modification of pH or temperature, within the prior art guidelines, to obtain optimal results, is considered *prima facie* obvious to the worker of ordinary skill in the art at the time the invention was made. [Answer, pages 8-9.]

However, the prior art methods differ from the claimed method in more than just pH and temperature. Only Casu (a) discloses the claimed periodate oxidation step, neither Casu nor Fransson (M) disclose (b) partial alkali depolymerization followed by (c) sodium borohydride reduction in combination, and (d) although both Fransson (M) and Casu disclose fractionated recovery of heparin degradation products, neither discloses or suggests (e) specific recovery of products having a molecular weight not less than that of the starting heparin material. Not only is the examiner's statement of the differences between the prior art and the claimed invention lacking, but also it is unclear how the examiner proposes to modify and/or combine the disclosures of Fransson (M) and/or Casu to arrive at the claimed invention. Whether or not the examiner considers a particular claim limitation "critical" or not, all of the claimed limitations should be addressed to establish a *prima facie* case of obviousness.

Based on the foregoing, we conclude that the examiner has failed to establish a *prima facie* case of obviousness as to claims 13-16.

CONCLUSION

To summarize, the decisions of the examiner (i) to reject claims 14 and 16 under 35 U.S.C. § 112 second paragraph, as indefinite, (ii) to reject claims 12 and 17 under 35 U.S.C. § 102 as anticipated by or, in the alternative, under 35 U.S.C. § 103 as being unpatentable over any of Naggi ‘063, Naggi ‘881 or Petitou, and (iii) to reject claims 13-16 under 35 U.S.C. § 103 as being unpatentable over either Fransson (M) or Casu are *reversed*.

REVERSED

WILLIAM F. SMITH Administrative Patent Judge	)
TEDDY S. GRON Administrative Patent Judge	) BOARD OF PATENT) APPEALS) AND) INTERFERENCES

CAROL A. SPIEGEL)
Administrative Patent Judge)

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